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Introduction to Beryllium: Uses, Regulatory History, and Disease

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Beryllium is an ubiquitous element in the environment, and it has many commercial applications. Because of its strength, electrical and thermal conductivity, corrosion resistance, and nuclear properties, beryllium products are used in the aerospace, automotive, energy, medical, and electronics industries. What eventually came to be known as chronic beryllium disease (CBD) was first identified in the 1940s, when a cluster of cases was observed in workers from the fluorescent light industry. The U.S. Atomic Energy Commission recommended the first 8-hour occupational exposure limit (OEL) for beryllium of 2.0 $\mu g/m^3$ in 1949, which was later reviewed and accepted by the American Conference of Governmental Industrial Hygienists® (ACGIH®), the American Industrial Hygiene Association (AIHA), the American National Standards Institute (ANSI), the Occupational Safety and Health Administration (OSHA), and the vast majority of countries and standard-setting bodies worldwide. The 2.0 $\mu g/m^3$ standard has been in use by the beryllium industry for more than 50 years and has been considered adequate to protect workers against clinical CBD. Recently, improved diagnostic techniques, including immunological testing and safer bronchoscopy, have enhanced our ability to identify subclinical CBD cases that would have formerly remained unidentified. Some recent epidemiological studies have suggested that some workers may develop CBD at exposures less than 2.0 $\mu g/m^3$. ACGIH is currently reevaluating the adequacy of the current 2.0 $\mu g/m^3$ guideline, and a plethora of research initiatives are under way to provide a better understanding of the cause of CBD. The research is focusing on the risk factors and exposure metrics that could be associated with CBD, as well as on efforts to better characterize the natural history of CBD. There is growing evidence that particle size and chemical form may be important factors that influence the risk of developing CBD. These research efforts are expected to provide data that will help identify a scientifically based OEL that will protect workers against CBD.

Keywords Beryllium, Industrial Hygiene, Occupational Exposure Limit, Occupational Medicine, Chronic Beryllium Disease, Beryllium Sensitization, Toxicology

Beryllium was not known to have presented a health hazard until it was used for industrial purposes. Chronic beryllium disease (CBD) was first associated with occupational exposure to beryllium in the 1940s when a cluster of cases was observed in workers from the fluorescent light industry.[1] Occupational exposure limits (OELs) for beryllium have been applied in the occupational environment for more than 50 years and have been used in U.S. regulations for nearly 30 years. The efficacy of the current beryllium standard of 2.0 $\mu g/m^3$ has been questioned as a result of recent epidemiological studies that suggest some workers may develop CBD at exposures less than 2.0 $\mu g/m^3$.[2–4] This article presents a review of (1) the occurrence in nature and industrial uses of beryllium, (2) the regulatory history of beryllium, (3) the historical and current understanding of the etiology of CBD, and (4) current and future research initiatives that are intended to characterize the risk factors associated with CBD.

NATURAL AND ANTHROPOGENIC BERYLLIUM

First discovered in 1798, beryllium is a naturally occurring element that is present in the earth's crust.[5] Because it is ubiquitous, beryllium is found in coal, wood, foodstuffs, and gemstones such as aquamarine and emerald.[6] The general population is exposed to naturally occurring beryllium from ambient air, drinking water, and diet on a daily basis. Average ambient concentrations of beryllium in soil range from 2.8 to 5 mg/kg.[6] The average ambient concentration in air in the United States is 0.00003 $\mu g/m^3$, while the median concentration in cities is 0.0002 $\mu g/m^3$.[7]

Concentrations of beryllium in drinking water range from 10 to 1,220 ng/L with an average of 190 ng/L.[8] The U.S. Environmental Protection Agency (EPA) has estimated that within the United States, the burning of coal and fuel oil accounts for 97.1 percent of beryllium released into the atmosphere, natural sources such as windblown dust and volcanic activity account

for 2.7 percent, and beryllium production accounts for about 0.2 percent.[9] Beryllium has been measured in rice at 80 μg/kg, bread at 330 μg/kg, and potatoes at 0.3 μg/kg.[6] The daily intake of beryllium by nonoccupationally exposed persons from food and water is approximately 0.52 μg per day with negligible exposures from ambient air.[10] The average burden of beryllium in nonoccupationally exposed persons is 0.20 mg/kg in the lung, whereas beryllium concentrations in other organs are typically below 0.08 mg/kg.[11]

BERYLLIUM AND ITS USES

Beryllium has been an essential material in the manufacture of products for the aerospace, automotive, energy, defense, medical, and electronics industries for more than half a century. It is a unique material exhibiting physical and mechanical properties unmatched by any other metal. Beryllium is one-third lighter than aluminum, making it one of the lowest-density metals. It is also one of the most rigid with a specific stiffness six times greater than steel. It possesses high heat-absorbing capability and has dimensional stability over a wide range of temperatures. Because of its unique combination of qualities, beryllium has become an increasingly important material for a range of commercial activities.[5] For example, it is present in virtually every cellular phone.

Today, the extraction of beryllium begins with the raw materials (bertrandite ore and/or beryl ore) (Figure 1). The extraction process for beryl ore involves melting, fritting, and grinding of the ore followed by reacting it with sulfuric acid to produce water soluble sulfate. The bertrandite ore is crushed into a slurry and leached with sulfuric acid at temperatures near the boiling point. The sulfate solutions undergo a series of solvent extraction steps ultimately producing beryllium hydroxide. The hydroxide is the common input material for copper-beryllium alloy, beryllium oxide ceramics, and pure beryllium metal manufacturing.[5]

The commercial value of beryllium became recognized in 1926, when beryllium-copper-nickel alloy was patented.[1] Application of copper-beryllium alloys, beryllium oxide, and metallic beryllium grew during World War II and, today, beryllium is used in the aerospace, automotive, energy, defense, medical, and electronics industries.[1] The estimated global market value for beryllium-containing materials is approximately $700 million per year.

Beryllium is a strategic and critical material for many industries and poses no special health risk in solid form, which is the form the public uses.[11] The beryllium industry produces three primary forms of beryllium: beryllium alloy (copper beryllium) is the largest, followed by beryllium metal, with beryllia ceramics (beryllium oxide) third.[5] Beryllium alloys with metals such as copper, nickel, or aluminum have high strength and hardness. Depending on the desired strength and electrical conductivity, copper-beryllium wrought products typically contain 0.15 percent to 2.0 percent beryllium. Copper-beryllium alloys for engineered materials are common in the electronics, automotive, defense, and aerospace industries because of their unique properties of strength, electrical and thermal conductivity, magnetic transparency, and corrosion resistance.[5] These three primary forms of beryllium-containing materials are used as critical, high-reliability elements in products such as air bag sensors, fire extinguisher sprinkler heads, x-ray windows for mammography, medical laser bores, pacemakers, landing-gear bearings, and weather satellites.[5]

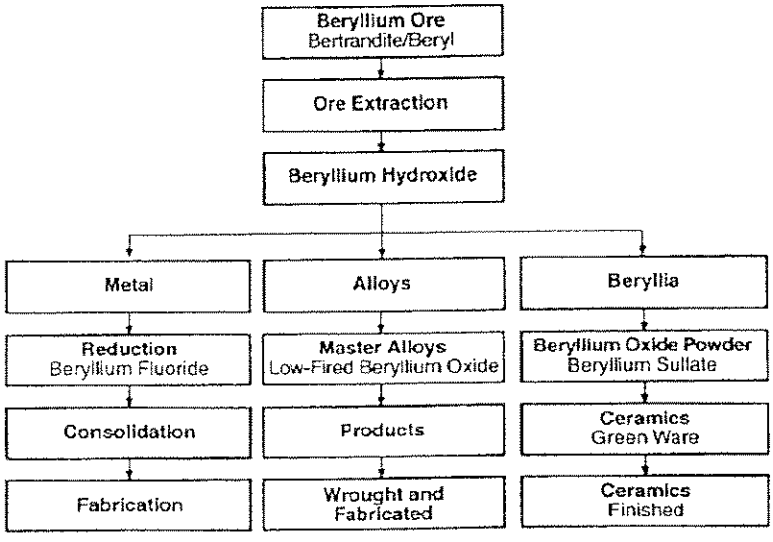

FIGURE 1
Overview of beryllium operations at extraction and refining facilities.

Copper beryllium is used in auto electronics, including the ignition control systems of many modern automobiles to increase gas mileage, thereby reducing air pollution. Copper-beryllium products are integral for both wired and wireless communications, such as cellular phones. Other applications include computers, oil exploration equipment, aircraft landing gear bushings and bearings, and plastic injection molding dies.

High beryllium content products (40–100% beryllium) are used in the military for advanced electro-optical targeting and infrared countermeasure devices, missile, and radar systems. Many of the advanced surveillance satellites also contain beryllium structures and electronic components. Beryllium metal is also used in fusion reactors and in the construction of nuclear devices for defense applications because of its nuclear and mechanical properties.[5] Because beryllium metal is transparent to x-rays, it is widely used as the window on high-resolution x-ray machines used for mammography.

Beryllium ceramics, produced from high-purity beryllium oxide powder (99.5%), are used in laser and electronic applications and for high-speed integrated circuits.[5]

MEDICAL AND REGULATORY HISTORY

Discovery of Chronic Beryllium Disease

Dr. H.S. Van Ordstrand of the Cleveland Clinic published in 1943 the first United States report of beryllium toxicity in workers, whom he had been seeing from two beryllium facilities located near Cleveland, Ohio.[12] He concluded that the beryllium salts and oxides were causing a serious acute lung reaction.[12] This report had less impact than it deserved because there was a publication released in that same year from the U.S. Public Health Service, which stated that beryllium is toxicologically inert.[13]

Nonetheless, the reports of respiratory and dermal illness among beryllium workers continued.[14,15] In 1946, Dr. Harriet Hardy and Dr. Irving Tabershaw concluded that a cluster of cases, of what was originally believed to be Boeck's Sarcoid in workers in the fluorescent light industry, was actually an illness resulting from exposure to phosphors of beryllium.[14] Their findings, describing what would later become known as CBD, were published in 1946. The identification of CBD among workers in the fluorescent light industry and the health concern of potential beryllium toxicity from use of florescent lights by the general public led to the fluorescent light industry terminating the use of beryllium-containing phosphor in fluorescent lights in 1949.[1,16]

Development of the Occupational Exposure Limit

Because beryllium is a necessary component for atomic weapons, the U.S. Atomic Energy Commission (AEC) became interested in the health risks associated with manufacturing beryllium. In 1947, Merril Eisenbud, Director of the AEC Health and Safety Laboratory, led an investigation, with voluntary participation from industry, to evaluate the occupational health hazards of beryllium. His investigation was undertaken to propose an OEL for AEC workers and subcontractors (Figure 2).[17,18]

The investigation resulted in a recommendation of three different standards. First, a permissible maximum peak exposure limit of 25 $\mu g/m^3$ over a 30-minute period was recommended to protect against acute beryllium disease, which was found to result from high exposures to beryllium salts or low-fired oxide.[17] Second, an ambient air standard of 0.01 $\mu g/m^3$ as a monthly average was recommended to protect the general public living near beryllium manufacturing facilities from CBD.[17] This community standard was prompted by a cluster of people in Lorain, Ohio, who developed CBD and who had not worked at the beryllium plant, but lived within 0.75 mile of the plant.[19] Results from a medical surveillance and exposure assessment survey of approximately 10,000 people in the Lorain community in 1948 indicated that people living within 0.25 mile of the beryllium plant were exposed to average beryllium air concentrations of 1 $\mu g/m^3$. Many of the neighborhood cases had close contact with family members or friends who worked at the plant and were likely exposed to contaminated work clothes, whereas others had no known association with beryllium workers.[19]

Third, a daily 8-hour time-weighted average (TWA) of 2.0 $\mu g/m^3$ was recommended as the OEL to protect against CBD.[17] This standard was established recognizing the generally accepted industrial hygiene concept that ambient air exposure standards are necessarily more stringent than occupational standards due to both the difference in exposure time (40 vs. 168 hours per week) and the greater vulnerability of the general public, which includes infants, the elderly, and those with severe health problems. The 2.0 $\mu g/m^3$ OEL for beryllium was based on the assumption that atom for atom, the toxicity of beryllium is comparable to that of heavy metals.[18] The OELs for other toxic metals, such as lead and mercury, were generally 100 $\mu g/m^3$. Therefore, in consideration of the fact that the atomic weight of these metals is approximately 200, which is about 20 times more than the atomic weight of beryllium, the typical metal OEL of 100 $\mu g/m^3$ was divided by 20 to account for the lower atomic weight of beryllium and divided again by 2.5 to account for the lack of understanding of CBD.[17,18] The 2.0 $\mu g/m^3$ OEL for beryllium that AEC originally adopted and recommended to contractors has been used for more than 50 years both in the United States and other countries.[17]

The AEC convened an Ad Hoc Advisory Committee, which included Merril Eisenbud and Dr. Harriet Hardy, among others, to consider whether the levels, already tentatively adopted as targets by AEC, should be accepted as permissible air level concentrations in beryllium installations having contracts with the AEC.[20] The advisory committee then examined the available data annually to evaluate whether the values should be maintained.[1] After several consecutive annual evaluations, the committee determined that there was no evidence to indicate that the proposed levels were not adequate to protect against beryllium disease and accepted the levels on a continuing basis.[1]

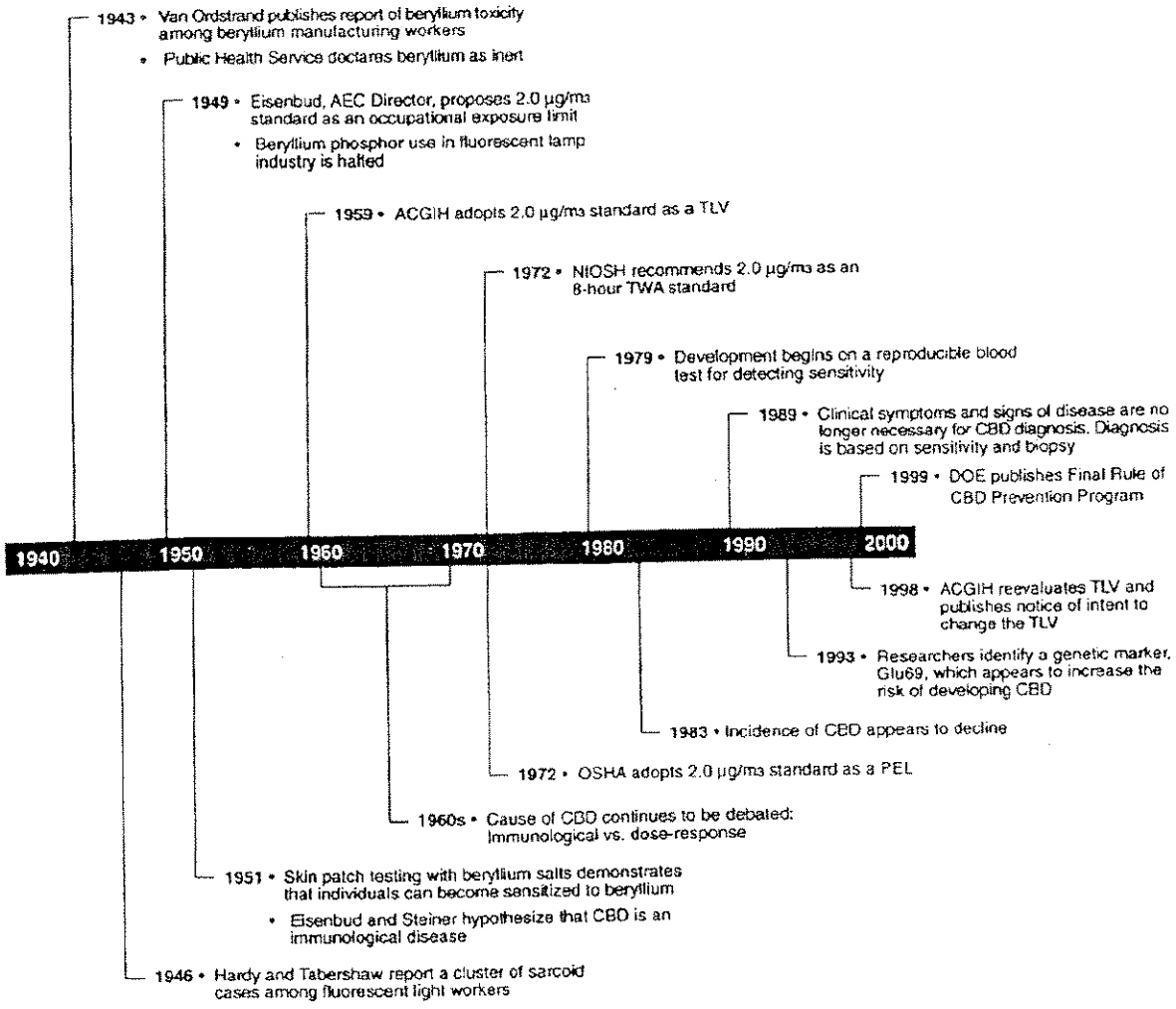

FIGURE 2
Medical and regulatory history of beryllium.

While this standard initially was perceived as overly conservative, the industrial hygiene control programs instituted in an attempt to comply to this OEL in the 1950s appeared to eliminate new cases of CBD for nearly 30 years.[21]

Adoption of the Standard

The 2.0 $\mu g/m^3$ beryllium standard, originally proposed and implemented by AEC, was eventually adopted by the American Conference of Governmental Industrial Hygienists®(ACGIH®) in 1959 as a Threshold Limit Value®(TLV®), by the American Industrial Hygiene Association (AIHA) in 1956 as a hygienic guide, and by the American National Standards Institute (ANSI) as a consensus standard in 1970. The Occupational Safety and Health Administration (OSHA) adopted the ANSI version as a permissible exposure limit (PEL) in 1972. Though OSHA specified that this airborne concentration should not be exceeded on a daily basis, the original implementation of the standard was to monitor exposures by calculating estimates of daily weighted averages (DWAs) over a quarterly period.[17] In 1956, AEC issued formal recommendations for the control of beryllium hazards, which included use of DWAs for exposure monitoring in the workplace. DWA exposures for a working day incorporate quarterly average measurements based on time studies of individual jobs and worker-specific tasks, which indicates that the standard was intended as an upper limit to the average exposure over an extended duration.[17]

For many years, some scientists believed that the 2.0 $\mu g/m^3$ standard was overly conservative and were of the opinion that the standard could be raised.[17] During the 1960s, the adequacy of the standard was formally re-evaluated a few times in published

papers and at scientific symposia.[22–24] The re-evaluation was based on three points. First, after adoption of the standard and significant reduction of exposures to airborne beryllium, the incidence of acute beryllium disease was almost nonexistent; second, the incidence of CBD had declined dramatically; and third, decreases in the disease rate were occurring despite the fact that the standard was not routinely met in facilities using beryllium. The discussions to raise the standard appeared to have consensus approval, but in every case the 2.0 $\mu g/m^3$ standard was retained because of a lack of data upon which to base a new number.

The Issue of Particle Size Testing

Because CBD is a granulomatous lung disease confined primarily to the respiratory region of the lung, it has been proposed by some scientists that CBD is not caused by particles greater than 10 μm in diameter, which are unable to deposit in the tracheobronchial region of the lung. Therefore, in the 1960s, discussions were held to decide whether conducting air sampling according to particle size (e.g., respirable versus nonrespirable) was necessary.[25] In June 1972, the National Institute for Occupational Safety and Health (NIOSH) issued its Criteria Document recommending the 2.0 $\mu g/m^3$ (total suspended particulate [TSP]), 8-hour per day TWA standard.[26]

In 1974, NIOSH, in cooperation with Brush Wellman Inc., conducted a comparison study of air sampling methods for beryllium. NIOSH reported significant differences between personal TSP and personal respirable particle measurements (those less than 10 μm).[27] As a result, NIOSH recommended sampling of all beryllium airborne particles because it was believed that sampling for only the respirable fraction eased the standard of protection (i.e., it would be easier to achieve 2.0 $\mu g/m^3$ based on only the respirable fraction).[26] Interestingly, the ANSI standard, as adopted by OSHA in 1972, applies only to insoluble dusts 5 μm in diameter or less. The ANSI standard further states that if particle size is not determined, the limits apply to all airborne dusts.

It was the late 1990s before the issue of particle size rematerialized, albeit in a different form. Some researchers suggested the dose-response relationship between beryllium exposure and CBD might be obscured by TSP measurements.[2,28] It has been hypothesized that aerosol characteristics, such as particle size, chemical form of beryllium, morphology, and surface chemistry may contribute to risk of CBD. A preliminary investigation of particle size characteristics in various beryllium process areas suggested that prevalence of CBD appeared to correlate with airborne concentrations of respirable particles and not total particle mass.[28] It was observed that the particle size characteristics varied depending on the type of beryllium process. For process areas that were associated with a size distribution of particles greater than 5 μm, there were fewer reported cases of CBD and sensitization compared to process areas that measured the greatest distribution of particles less than 5 μm.[28] Therefore, it was hypothesized that sampling respirable particles may be a better predictor (exposure metric) for CBD than total mass of airborne beryllium particles. Additional studies are needed to validate these preliminary findings and to determine an appropriate sampling method. Together, these studies could form the basis for an OEL based on particle size and chemical form of beryllium.

OSHA's Cancer Policy

In 1975, OSHA published a cancer policy, the so-called "Generic Cancer Policy," which required that any chemical that induces tumors in two or more animal species be regulated as a carcinogen with a PEL at the lowest level attainable.[29] Given this policy, OSHA proposed to reduce the beryllium standard to 1.0 $\mu g/m^3$ 8-hour TWA, based on the presumption that beryllium was a carcinogen.[29] Industry argued that the proposed beryllium standard was based on poor animal data on carcinogenicity. The U.S. Supreme Court decision, referred to as the "1980 benzene decision," resulted in a requirement that any standard promulgated by OSHA that is more stringent than the current standard must provide evidence that significant risk in the workplace does exist under the current standard and that the proposed standard must reduce the risk.[30] As a result, OSHA never promulgated the beryllium cancer standard.

Over the past several years, the International Agency for Research on Cancer, the National Toxicology Program, and ACGIH have listed beryllium as a carcinogen.

In commenting on the change in carcinogenicity classification, ACGIH stated,

> "the weight of the evidence supports the view that beryllium is a confirmed human carcinogen but is of such low potency that only persons exposed at levels similar to those that existed in the Lorain and Reading plants in the 1940s would be at significant risk of developing lung cancer."

It is important to note that levels in the 1940s ranged from about 100 to 10,000 times higher than the levels typically experienced today. There remains considerable debate within the scientific community whether exposure to beryllium has ever caused cancer in humans.[31]

Concerns About the OEL Raised by Recent Epidemiological Data

When development of improved medical tests allowed researchers to identify asymptomatic persons as having CBD, the effectiveness of the OEL for beryllium began to be questioned.[2–4,32] In 1998, ACGIH published a notification of intent to decrease the TLV to 0.2 $\mu g/m^3$, which was prompted by recent epidemiological studies that suggest cases of CBD had been detected in workers exposed to workplace concentrations below 2.0 $\mu g/m^3$.[7] Since then, various scientists have noted that these studies may suggest that the 2.0 $\mu g/m^3$ standard may not be as protective as once thought; however, it was premature to assume that simply lowering the OEL for TSP of beryllium

would reduce the incidence of disease, because a clear dose-response relationship between beryllium exposure and prevalence of CBD is lacking.[33]

There are a number of difficulties in interpreting the various epidemiology studies, which make identification of a so-called safe level of exposure a difficult task. For example, the scientific community, including the Environmental Protection Agency (EPA) and the U.S. Department of Energy (DOE), has noted numerous uncertainties associated with exposure estimates of beryllium workers reported in the epidemiological studies.[34] A recent review by DOE stated

> "High day-to-day variation in exposure level and excursions above the 2 $\mu g/m^3$ limit have occurred in all groups studied. Excursions make up a significant contribution to individuals' total doses, confounding attempts to understand if dose rate is an important risk factor."[34]

Other shortcomings include improper use of air sampling data to estimate worker exposures. Use of general area air sampling data in some studies has been treated as equivalent to breathing zone measurements of the individual workers[4,35] and average grouped worker exposures have historically been used when OSHA requires that exposure estimates of individual workers be compared to the standard.[3] It has been argued that exposure estimates based on airborne measurements associated with grouped job categories or from area measurements do not give an accurate assessment of exposure to individual workers, and therefore, may not provide a clear understanding of the relationship between exposure to beryllium and CBD. Consequently, it is important that studies upon which a new OEL will be based use air sampling measurements that are relevant to individual worker exposures.

CHRONIC BERYLLIUM DISEASE

The pathogenesis of CBD is thought to involve lymphocytic response to beryllium particles recognized as an antigen, followed by cell proliferation, release of immune cell mediators, and accumulation of inflammatory cells in the lung, leading to the development of granulomatous lesions.[36] Merril Eisenbud and James Sterner first hypothesized in 1951 that CBD was an immunological disease.[37] The basis of this hypothesis originated from epidemiological evidence that (1) disease is observed at low airborne concentrations, (2) beryllium concentrations in tissues do not correlate with severity of disease, (3) CBD may develop several years following termination of beryllium exposure, (4) delayed skin test reactivity occurs in humans, and (5) CBD is a granulomatous reaction.[37] It took decades for Eisenbud's immune response model to become generally accepted by the scientific community.

Sensitization Testing

Skin patch testing with beryllium salts, which was conducted in the 1950s, was the first experimental evidence that indicated that individuals can become sensitized to beryllium.[38,39] Subsequently, in vitro immunological testing has been used to identify beryllium-sensitized individuals, which then allowed for the targeted use of bronchoscopy in the detection of primarily asymptomatic CBD cases.[40–42] It is believed, although the evidence is lacking, that beryllium sensitization precedes the development of CBD in the lung. Not all persons sensitized will develop CBD. The most recent study of sensitization testing using the blood lymphocyte proliferation test (BLPT) evaluated the value of BLPT as a screening tool by assessing the reliability as well as its accuracy with respect to predicting CBD. The investigators concluded that substantial inter- and intra-laboratory disagreement exists mong the laboratories that conduct this test and the test overall had a positive predictive value of 40–50 percent for CBD.[43] It is generally agreed that the BLPT by itself is not diagnostic; however, despite its limitations, the BLPT remains a useful disease surveillance tool.[43]

Diagnostic Criteria

Diagnosis of CBD has historically relied upon medical history, physical examination, chest x-ray, and pulmonary function testing.[36,44] Beginning in the late 1980s, development of immunological tests to identify beryllium sensitization, such as the BLPT and the bronchoalveolar lavage lymphocyte proliferation test (BALLPT), in conjunction with more sophisticated medical devices for examination of the lungs, including the fiberoptic bronchoscope, enhanced the medical community's ability to identify early stages of the disease.[36,44] With the use of these tools, it was soon recognized that a person can have CBD without clinical symptoms or abnormal chest x-ray or lung function tests. Today, the diagnostic criteria for CBD that are used by Brush Wellman Inc. are the confirmed sensitization to beryllium and presence of pulmonary granulomas in lung biopsies (obtained during bronchoscopy). Beryllium sensitization is defined as two positive BLPT's over any time period. If a person is identified as beryllium-sensitized, the BALLPT and transbronchial lung biopsies are performed at the discretion of the worker.[36,44] Although not all referred workers agree to have the bronchoscopy performed, these new tools enhance the ability to identify cases of asymptomatic CBD, which could not have been identified or reported prior to the late 1980s.

Genetic Disposition

While many aspects of the etiology of CBD are still unclear, researchers have identified a genetic marker that appears to significantly increase the probability that a worker will develop CBD. Saltini and colleagues, who were originally searching for a genetic marker for sarcoidosis, found that the presence of Glu69 increased the risk of CBD.[45,46] To date, studies have not confirmed Glu69 to be the only marker. While about 75 percent of those with CBD have Glu69 in their blood,[47,48] only about 40 percent of those sensitized are positive for the Glu69 marker (unpublished). The 40 percent rate for the sensitized group is about the same as for the general population.[49] Studies of

Richeldi and co-workers have shown that presence of the Glu69 marker was associated with an eightfold increase in the rate of CBD in workers with a history of higher exposure to beryllium, thereby suggesting that genetic and exposure factors may have an additive or multiplicative effect.[48]

Because the role of the Glu69 gene in the development of CBD is not well understood and a significant portion of the general population express the genetic marker, future research is needed on these and other issues before it can be determined if definitive genetic tests will be predictive of CBD. Strategies for future use of such tests will need to be devised in such a manner so as not to discriminate against certain workers.

Risk Factors

While the general population is exposed to beryllium in drinking water and foodstuffs on a daily basis, no known cases of CBD in the general public have been reported following exposure to materials containing beryllium in nature. In 1995, a workshop held in the United States by the Beryllium Industry Scientific Advisory Committee and representatives of the five U.S. laboratories that perform BLPTs conducted an informal poll identifying 5–6 positive BLPTs (1% of the tested populations) out of a control group of about 500 persons with no known occupational exposure to beryllium. No cases have been reported from the use of beryllium in consumer applications. Most uses in consumer applications pose limited potential for exposure because either the beryllium-containing part or structure is not easily accessible or the part remains as a solid structure through its useful life.

No cases of CBD have been reported among workers who have worked exclusively in beryllium ore mining operations.[50] Cases have occurred in worker populations involved in recycling beryllium-containing materials. These observations suggest that workers with exposure to beryllium metal, alloy, or oxide, and not the beryllium ores (i.e., bertrandite and beryl), are the group at risk of CBD. In addition, the observation that beryllium oxides are not generated in manufacturing processes until after the mining-related processing of ore to beryllium hydroxide suggests that some level of exposure to beryllium oxide may be necessary to develop the disease.

There are potentially several factors that influence the probability that workers exposed to beryllium will develop CBD. Presenters at the symposium, "Beryllium: Effect on Worker Health" addressed some of the issues, including (1) genetic susceptibility, (2) varying risks for different manufacturing processes, (3) different toxicities of different forms of beryllium, (4) particle size, and (5) pulmonary and extrapulmonary exposure pathways as possible contributors to the risk of CBD.[28,51–53] Currently, it is unknown whether CBD cases are attributable to failure of the OSHA PEL or ACGIH TLV to protect worker health, whether certain airborne characteristics within the current 2.0 $\mu g/m^3$ standard (e.g., particle size, morphology, beryllium form) dictate the risk, or whether failure to consistently maintain workplace concentrations below the OEL are the reason why cases of CBD continue to occur.

RESEARCH INITIATIVES

Several research investigations have been initiated to evaluate the relationship between beryllium exposure to workers and CBD. The Beryllium Industry Science Advisory Committee, Brush Wellman Inc., NIOSH, DOE, including the Los Alamos National Laboratory and the Lawrence Livermore National Laboratory, and other organizations are currently conducting research efforts to (1) characterize the risk factors associated with CBD, (2) identify the most relevant exposure metrics, (3) characterize the natural history of CBD, and (4) evaluate the effectiveness of medical surveillance and treatment programs. One research program conducted jointly by Brush Wellman Inc. and NIOSH involves a cross-sectional epidemiological study at Brush Wellman Inc.'s Elmore, Ohio, Reading, Pennsylvania, and Tucson, Arizona, manufacturing plants along with characterization of aerosols at these facilities to identify exposure metrics that are associated with disease. One of the primary objectives of these research efforts is to provide scientific data for identification of a scientifically sound OEL that will prevent beryllium disease.

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